	Type	L #	Hits	Search Text
1	BRS	L1	81	co-repressor or corepressor
2	BRS	L6	848	"retinoic acid receptor" or "thyroid hormone receptor"
3	BRS	L11	22	1 and 6
4	BRS	L16	12	1 same 6

09/522,723
Paper # 10 Attach

09/522,753

Paper #10 Attach

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FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE' ENTERED AT 19:56:49 ON 04 OCT 2001

L1 19061 RETINOIC ACID RECEPTOR OR THYROID HORMONE RECEPTOR
L2 3880 CO-REPRESSOR OR COREPRESSOR OR "CO REPRESSOR"
L3 672 L1 (P) L2
L4 600 L1 (S) L2
L5 309 SMRT AND L4
L6 101 DUP REM L5 (208 DUPLICATES REMOVED)
L7 60 L6 AND PY<2000
L8 1 L7 AND PY< 1996
L9 11636 (EVANS R? OR EVANS, R?)/AU,IN
L10 38247 (CHEN J? OR CHEN, J?)/AU,IN
L11 45 (ORDENTLICH P? OR ORDENTLICH, P?)/AU,IN
L12 356 (DOWNES M? OR DOWNES, M?)/AU,IN
L13 157 L2 AND (L9 OR L10 OR L11 OR L12)
L14 47 DUP REM L13 (110 DUPLICATES REMOVED)
L15 92 DUP REMOVE L14 L7 (15 DUPLICATES REMOVED)

L15 ANSWER 11 OF 92 MEDLINE

AB The t(5;17) variant of acute promyelocytic leukemia (APL) fuses the genes for nucleophosmin (NPM) and the retinoic acid receptor alpha (RARalpha). Two NPM-RAR molecules are expressed as a result of alternative RNA splicing. Both contain RARalpha sequences that encode the DNA binding, heterodimerization, and ligand activation domains of RARalpha. This study was designed to test the ability of these fusion proteins to act as transcriptional activators of retinoic acid responsive promoters. The NPM-RAR fusion proteins bind to retinoic acid response element sequences as either homodimers or as heterodimers with RXR. Transcription of retinoic acid-inducible promoters is activated by the fusion proteins in the presence of retinoic acid. The level of transactivation induced by the NPM-RAR fusions differs from the level of transactivation induced by wild-type RARalpha in both a promoter and cell specific fashion, and more closely parallels the pattern of activation of the PML-RAR fusion than wild-type RARalpha. In addition, NPM-RAR decreases basal transcription from some promoters and acts in a dominant-negative fashion when co-transfected with wild-type RARalpha. Both NPM-RAR and PML-RAR interact with the co-repressor protein SMRTe in a manner that is less sensitive than RARalpha to dissociation by retinoic acid. Retinoic acid induces binding of the co-activator protein RAC3. These data indicate that the NPM-RAR fusion proteins can modulate expression of retinoid-responsive genes in a positive or negative manner, depending on context of the promoter, and lend support to the hypothesis that aberrant transcriptional activation underlies the APL phenotype. (Blood. 2000;95:2683-2690)

ACCESSION NUMBER: 2000218755 MEDLINE

DOCUMENT NUMBER: 20218755 PubMed ID: 10753851

TITLE: The t(5;17) acute promyelocytic leukemia fusion protein NPM-RAR interacts with co-repressor and co-activator proteins and exhibits both positive and negative transcriptional properties.

AUTHOR: Redner R L; Chen J D; Rush E A; Li H; Pollock S L

CORPORATE SOURCE: Division of Hematology/Oncology, Department of Medicine, University of Pittsburgh Medical Center, PA 15213, USA.. redner+@pitt.edu

CONTRACT NUMBER: R29 CA67346 (NCI)

SOURCE: BLOOD, (2000 Apr 15) 95 (8) 2683-90. Journal code: A8G; 7603509. ISSN: 0006-4971.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200005

ENTRY DATE: Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000505

L15 ANSWER 17 OF 92 CAPLUS COPYRIGHT 2001 ACS

AB The invention is related to the use of histone deacetylase inhibitors as activators of genes responsive to hormone receptors and to counteract the oncogenic functions of oncogenic proteins. Histone deacetylase relieves repressed systems and, when in combination with a ligand for a member of the steroid/thyroid hormone superfamily, the differentiation effects of retinoids are enhanced. Formulations for modulating hormone-mediated

processes and assays for the identification of potential modulators are presented.

ACCESSION NUMBER: 1999:325757 CAPLUS
DOCUMENT NUMBER: 130:332877
TITLE: Methods for the use of inhibitors of co-repressors for the treatment of neoplastic diseases
INVENTOR(S): Evans, Ronald M.; Lin, Richard J.; Nagy, Laszlo
PATENT ASSIGNEE(S): The Salk Institute for Biological Studies, USA
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9923885	A1	19990520	WO 1998-US23962	19981110
AU 9913959	A1	19990531	AU 1999-13959	19981110
EP 1037533	A1	20000927	EP 1998-957781	19981110

R: CH, DE, FR, GB, LI
PRIORITY APPLN. INFO.: US 1997-966876 A2 19971110
WO 1998-US23962 W 19981110
REFERENCE COUNT: 6
REFERENCE(S): (1) Chen; Blood 1994, V84(7), P2122 CAPLUS
(2) Chen; Nature 1995, V377(5), P454
(3) Horlein; Nature 1995, V377(5), P397
(4) President and Fellows of Harvard College; WO 97/35990 A2 1997 CAPLUS
(5) Sucov; US 5091518 A 1992 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 18 OF 92 MEDLINE
AB Thyroid hormone receptors (T3Rs) are hormone-regulated transcription factors. Different T3R isoforms are expressed in a tissue-specific and developmentally regulated manner. The T3Ralpha-1, beta-0, and beta-1 isoforms typically repress target gene expression in the absence of hormone and activate transcription in the presence of hormone. Intriguingly, however, the T3Rbeta-2 isoform fails to repress, and instead is able to activate transcription in both the absence and presence of hormone. We investigated the molecular mechanism behind this absence of repression by T3Rbeta-2. Repression by T3Ralpha-1, beta-0, and beta-1 is mediated by the ability of these isoforms to physically recruit a SMRT/N-CoR corepressor complex. We determined that the unliganded T3Rbeta-2 also recruits the SMRT corepressor; in contrast to the alpha-1, beta-0, and beta-1 isoforms, however, the T3Rbeta-2 protein interacts not only with the C-terminal "receptor-interaction domain" of SMRT, but also makes additional contacts with the N-terminal "silencing domain" of the SMRT corepressor. These additional, T3Rbeta-2-specific contacts interfere with the subsequent association of SMRT with mSin3, a crucial second subunit of the corepressor holo-complex. Our results suggest that T3Rbeta-2 regulates transcription through a novel anti-repression mechanism, recruiting SMRT, but preventing the

subsequent formation of a functional corepressor complex.
ACCESSION NUMBER: 2000069698 MEDLINE
DOCUMENT NUMBER: 20069698 PubMed ID: 10601274
TITLE: Transcriptional anti-repression. Thyroid hormone receptor beta-2 recruits SMRT corepressor but interferes with subsequent assembly of a functional corepressor complex.
AUTHOR: Yang Z; Hong S H; Privalsky M L
CORPORATE SOURCE: Section of Microbiology, Division of Biological Sciences, University of California, Davis, California 95616, USA.
CONTRACT NUMBER: R37 CA-53394 (NCI)
RO1 DK-53528 (NIDDK)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Dec 24) 274 (52) 37131-8.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000124
Last Updated on STN: 20000124
Entered Medline: 20000113

L15 ANSWER 19 OF 92 MEDLINE
AB Hypermethylated in cancer (HIC-1), a new candidate tumor suppressor gene located in 17p13.3, encodes a protein with five C(2)H(2) zinc fingers and an N-terminal broad complex, tramtrack, and bric a brac/poxviruses and zinc-finger (BTB/POZ) domain found in actin binding proteins or transcriptional regulators involved in chromatin modeling. In the human B cell lymphoma (BCL-6) and promyelocityc leukemia (PLZF) oncoproteins, this domain mediates transcriptional repression through its ability to recruit a silencing mediator of retinoid and thyroid hormone receptor (SMRT)/nuclear receptor corepressor (N-CoR)-mSin3A-histone deacetylase (HDAC) complex, a mechanism shared with numerous transcription factors. HIC-1 appears unique because it contains a 13-aa insertion acquired late in evolution, because it is not found in its avian homologue, gammaF1-binding protein isoform B (gammaFBP-B), a transcriptional repressor of the gammaF-crystallin gene. This insertion, located in a conserved region involved in the dimerization and scaffolding of the BTB/POZ domain, mainly affects slightly the ability of the HIC-1 and gammaFBP-B BTB/POZ domains to homo- and heterodimerize in vivo, as shown by mammalian two-hybrid experiments. Both the HIC-1 and gammaFBP-B BTB/POZ domains behave as autonomous transcriptional repression domains. However, in striking contrast with BCL-6 and PLZF, both HIC-1 and gammaFBP-B similarly fail to interact with members of the HDAC complexes (SMRT/N-CoR, mSin3A or HDAC-1) in vivo and in vitro. In addition, a general and specific inhibitor of HDACs, trichostatin A, did not alleviate the HIC-1- and gammaFBP-B-mediated transcriptional repression, as previously shown for BCL-6. Taken together, our studies show that the recruitment onto target promoters of an HDAC complex is not a general property of transcriptional repressors containing a conserved BTB/POZ domain.
ACCESSION NUMBER: 2000079567 MEDLINE
DOCUMENT NUMBER: 20079567 PubMed ID: 10611298

TITLE: Recruitment of SMRT/N-CoR-mSin3A-HDAC-repressing complexes is not a general mechanism for BTB/POZ transcriptional repressors: the case of HIC-1 and gammaFBP-B.
AUTHOR: Deltour S; Guerardel C; Leprince D
CORPORATE SOURCE: Centre National de la Recherche Scientifique Unite Mixte de Recherche 8526, Institut de Biologie de Lille, Institut Pasteur de Lille, 1 Rue Calmette, 59017 Lille Cedex, France.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Dec 21) 96 (26) 14831-6.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000127

L15 ANSWER 20 OF 92 MEDLINE
AB Homeobox (hox) proteins have been shown to regulate cell fate and segment identity by promoting the expression of specific genetic programs. In contrast to their restricted biological action in vivo, however, most homeodomain factors exhibit promiscuous DNA binding properties in vitro, suggesting a requirement for additional cofactors that enhance target site selectivity. In this regard, the pbx family of homeobox genes has been found to heterodimerize with and thereby augment the DNA binding activity of certain hox proteins on a subset of potential target sites. Here we examine the transcriptional properties of a forced hox-pbx heterodimer containing the pancreas-specific orphan homeobox factor pdx fused to pbx-1a. Compared to the pdx monomer, the forced pdx-pbx1a dimer, displayed 10- to 20-fold-higher affinity for a consensus hox-pbx binding site but was completely unable to bind a hox monomer recognition site. The pdx-pbx dimer stimulated target gene expression via an N-terminal trans-activation domain in pdx that interacts with the coactivator CREB binding protein. The pdx-pbx dimer was also found to repress transcription via a C-terminal domain in pbx-1a that associates with the corepressors SMRT and NCoR. The transcriptional properties of the pdx-pbx1 complex appear to be regulated at the level of alternative splicing; a pdx-pbx polypeptide containing the pbx1b isoform, which lacks the C-terminal extension in pbx1a, was unable to repress target gene expression via NCoR-SMRT. Since pbx1a and pbx1b are differentially expressed in endocrine versus exocrine compartments of the adult pancreas, our results illustrate a novel mechanism by which pbx proteins may modulate the expression of specific genetic programs, either positively or negatively, during development.
ACCESSION NUMBER: 2000036779 MEDLINE
DOCUMENT NUMBER: 20036779 PubMed ID: 10567547
TITLE: Pbx-Hox heterodimers recruit coactivator-corepressor complexes in an isoform-specific manner.
AUTHOR: Asahara H; Dutta S; Kao H Y; Evans R M; Montminy M
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston,

Massachusetts 02215, USA.
CONTRACT NUMBER: POI54418 (NIDDK)
ROIDK49777
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1999 Dec) 19 (12) 8219-25.
Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000114
Last Updated on STN: 20000114
Entered Medline: 20000106

L15 ANSWER 22 OF 92 MEDLINE DUPLICATE 2
AB SMRT (silencing mediator for retinoid and thyroid hormone receptors) and N-CoR (nuclear receptor copressor) mediate transcriptional repression of important regulators that are involved in many signaling pathways. SMRT and N-CoR are related proteins that form complexes with mSin3A/B and histone deacetylases to induce local chromatin condensation and transcriptional repression. However, SMRT is substantially smaller than N-CoR, lacking an N-terminal domain of approximately 1,000 aa that are present in N-CoR. Here, we report the identification of SMRT-extended (SMRTe), which contains an N-terminal sequence that shows striking similarity with N-CoR. As in N-CoR, this SMRTe-N-terminal domain also represses basal transcription. We find that SMRTe expression is regulated during cell cycle progression and SMRTe transcripts are present in many embryonic tissues. These data redefine a structurally and functionally more related nuclear receptor corepressor family and suggest an additional role for SMRTe in the regulation of cycle-specific gene expression in diverse signaling pathways.
ACCESSION NUMBER: 1999199215 MEDLINE
DOCUMENT NUMBER: 99199215 PubMed ID: 10097068
TITLE: SMRTe, a silencing mediator for retinoid and thyroid hormone receptors-extended isoform that is more related to the nuclear receptor corepressor.
AUTHOR: Park E J; Schroen D J; Yang M; Li H; Li L; Chen J D
CORPORATE SOURCE: Departments of Pharmacology and Molecular Toxicology, Molecular Cell Biology and Cancer Center, University of Massachusetts Medical School, Worcester, MA 01655, USA.
CONTRACT NUMBER: DK52542 (NIDDK)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Mar 30) 96 (7) 3519-24.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF125671; GENBANK-AF125672
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990525
Last Updated on STN: 19990525
Entered Medline: 19990512

L15 ANSWER 23 OF 92 MEDLINE DUPLICATE 3
AB The association of transcription corepressors SMRT and N-CoR

with retinoid and thyroid receptors results in suppression of basal transcriptional activity. A key event in nuclear receptor signaling is the hormone-dependent release of corepressor and the recruitment of coactivator. Biochemical and structural studies have identified a universal motif in coactivator proteins that mediates association with receptor LBDs. We report here the identity of complementary acting signature motifs in SMRT and N-CoR that are sufficient for receptor binding and ligand-induced release. Interestingly, the motif contains a hydrophobic core (PhixxPhiPhi) similar to that found in NR coactivators. Surprisingly, mutations in the amino acids that directly participate in coactivator binding disrupt the corepressor association. These results indicate a direct mechanistic link between activation and repression via competition for a common or at least partially overlapping binding site.

ACCESSION NUMBER: 2000084997 MEDLINE
DOCUMENT NUMBER: 20084997 PubMed ID: 10617570
TITLE: Mechanism of corepressor binding and release from nuclear hormone receptors.
AUTHOR: Nagy L; Kao H Y; Love J D; Li C; Banayo E; Gooch J T; Krishna V; Chatterjee K; Evans R M; Schwabe J W
CORPORATE SOURCE: The Salk Institute for Biological Studies, Gene Expression Laboratory, La Jolla, California 92037 USA.
CONTRACT NUMBER: GM26444 (NIGMS)
HD27183 (NICHD)
SOURCE: GENES AND DEVELOPMENT, (1999 Dec 15) 13 (24) 3209-16.
Journal code: FN3; 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000127

L15 ANSWER 24 OF 92 MEDLINE
AB Retinoic acid and thyroid hormone receptors can act alternatively as ligand-independent repressors or ligand-dependent activators, based on an exchange of N-CoR or SMRT-containing corepressor complexes for coactivator complexes in response to ligands. We provide evidence that the molecular basis of N-CoR recruitment is similar to that of coactivator recruitment, involving cooperative binding of two helical interaction motifs within the N-CoR carboxyl terminus to both subunits of a RAR-RXR heterodimer. The N-CoR and SMRT nuclear receptor interaction motifs exhibit a consensus sequence of LXX I/H I XXX I/L, representing an extended helix compared to the coactivator LXXLL helix, which is able to interact with specific residues in the same receptor pocket required for coactivator binding. We propose a model in which discrimination of the different lengths of the coactivator and corepressor interaction helices by the nuclear receptor AF2 motif provides the molecular basis for the exchange of coactivators for corepressors, with ligand-dependent formation of the charge clamp that stabilizes LXXLL binding sterically inhibiting interaction of the extended corepressor helix.

ACCESSION NUMBER: 2000084996 MEDLINE
DOCUMENT NUMBER: 20084996 PubMed ID: 10617569

TITLE: Molecular determinants of nuclear receptor-corepressor interaction.
AUTHOR: Perissi V; Staszewski L M; McInerney E M; Kurokawa R; Krones A; Rose D W; Lambert M H; Milburn M V; Glass C K; Rosenfeld M G
CORPORATE SOURCE: University of California, San Diego (UCSD), Graduate Student, Molecular Pathology Program, UCSD, La Jolla, California 92095-0648 USA.
SOURCE: GENES AND DEVELOPMENT, (1999 Dec 15) 13 (24) 3198-208.
Journal code: FN3; 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000127

L15 ANSWER 25 OF 92 MEDLINE
AB Nuclear hormone receptors are ligand-regulated transcription factors that modulate the expression of specific target genes in response to the binding of small, hydrophobic hormone ligands. Many nuclear hormone receptors, such as the retinoic acid receptors , can both repress and activate target gene expression; these bimodal transcription properties are mediated by the ability of these receptors to tether auxiliary factors, denoted corepressors and coactivators. Corepressors are typically bound by receptors in the absence of cognate hormone, whereas binding of an appropriate hormone agonist induces an allosteric alteration in the receptor resulting in release of the corepressor and recruitment of coactivator. Structural analysis indicates that there is a close induced fit between the hormone ligand and the receptor polypeptide chain. This observation suggests that different ligands, once bound, may confer distinct conformations on the receptor that may invoke, in turn, distinct functional consequences. We report here that different retinoids do differ in the ability to release corepressor once bound to retinoic acid receptor and suggest that these differences in corepressor release may manifest as differences in transcriptional regulation.
ACCESSION NUMBER: 1999115634 MEDLINE
DOCUMENT NUMBER: 99115634 PubMed ID: 9915825
TITLE: Retinoid isomers differ in the ability to induce release of SMRT corepressor from retinoic acid receptor-alpha.
AUTHOR: Hong S H; Privalsky M L
CORPORATE SOURCE: Section of Microbiology, Division of Biological Sciences, University of California, Davis, California 95616, USA.
CONTRACT NUMBER: R37 CA-53394 (NCI)
RO1 DK-53528 (NIDDK)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Jan 29) 274 (5) 2885-92.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990316
Last Updated on STN: 19990316
Entered Medline: 19990303

L15 ANSWER 26 OF 92 MEDLINE DUPLICATE 4
AB Nuclear hormone receptors have been shown to repress transcription in the absence of ligand. This repression is mediated by a corepressor complex that contains the Sin3A protein and histone deacetylases (HDAC1 and 2). Studies by several groups demonstrate that this complex is recruited to nuclear receptors through the highly related corepressors SMRT (silencing mediator of retinoid acid and thyroid hormone receptor) and N-CoR (nuclear receptor corepressor). We describe here the cloning, characterization, and chromosomal mapping of forms of human and mouse SMRT that includes a 1,000-aa extension, which reveals striking homology to the amino terminus of N-CoR. Structure and function studies of wild-type and natural splicing variants suggest the presence of 3-4 amino terminal domains that repress in a cooperative as well as mechanistically distinct fashion.
ACCESSION NUMBER: 1999178941 MEDLINE
DOCUMENT NUMBER: 99178941 PubMed ID: 10077563
TITLE: Unique forms of human and mouse nuclear receptor corepressor SMRT.
AUTHOR: Ordentlich P; Downes M; Xie W; Genin A; Spinner N B; Evans R M
CORPORATE SOURCE: Gene Expression Laboratory, The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Mar 16) 96 (6) 2639-44. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF113001; GENBANK-AF113002; GENBANK-AF113003
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 19990601
Entered Medline: 19990520

L15 ANSWER 28 OF 92 MEDLINE
AB A distinguishing, but unexplained, characteristic of steroid hormone action is the dose-response curve for the regulation of gene expression. We have previously reported that the dose-response curve for glucocorticoid induction of a transfected reporter gene in CV-1 and HeLa cells is repositioned in the presence of increasing concentrations of glucocorticoid receptors (GRs). This behavior is now shown to be independent of the reporter, promoter, or enhancer, consistent with our proposal that a transacting factor(s) was being titrated by added receptors. Candidate factors have been identified by the observation that changes in glucocorticoid induction parameters in CV-1 cells could be reproduced by varying the cellular levels of coactivators [transcriptional intermediary factor 2 (TIF2), steroid receptor coactivator 1 (SRC-1), and amplified in breast cancer 1 (AIB1)], comodulator [CREB-binding protein

(CBP)], or corepressor [silencing mediator for retinoid and thyroid-hormone receptors (SMRT)] without concomitant increases in GR. Significantly, the effects of TIF2 and SMRT were mutually antagonistic. Similarly, additional SMRT could reverse the action of increased levels of GRs in HeLa cells, thus indicating that the effects of cofactors on transcription may be general for GR in a variety of cells. These data further indicate that GRs are yet an additional target of the corepressor SMRT . At the same time, these cofactors were found to be capable of regulating the level of residual agonist activity displayed by antiglucocorticoids. Finally, these observations suggest that a novel role for cofactors is to participate in processes that determine the dose-response curve, and partial agonist activity, of GR-steroid complexes. This new activity of cofactors is disconnected from their ability to increase or decrease GR transactivation. An equilibrium model is proposed in which the ratio of coactivator-corepressor bound to either receptor-agonist or -antagonist complexes regulates the final transcriptional properties.

ACCESSION NUMBER: 2000065644 MEDLINE
DOCUMENT NUMBER: 20065644 PubMed ID: 10598585
TITLE: Opposing effects of corepressor and coactivators in determining the dose-response curve of agonists, and residual agonist activity of antagonists, for glucocorticoid receptor-regulated gene expression.
AUTHOR: Szapary D; Huang Y; Simons S S Jr
CORPORATE SOURCE: National Institute of Diabetes and Digestive and Kidney Diseases, Laboratory of Molecular and Cellular Biology, National Institutes of Health, Bethesda, Maryland 20892-0805, USA.
SOURCE: MOLECULAR ENDOCRINOLOGY, (1999 Dec) 13 (12) 2108-21.
Journal code: NGZ; 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000124
Last Updated on STN: 20000124
Entered Medline: 20000110

L15 ANSWER 29 OF 92 MEDLINE

AB Complex physiological stimuli differentially regulate the tissue-specific transcription of the lipoprotein lipase (LPL) gene. A conserved DNA recognition element (-171 to -149 bp) within the promoter functions as a transcriptional enhancer when bound by the peroxisome proliferator-activated receptor-gamma2 (PPARgamma2)/retinoid X receptor alpha (RXRalpha) heterodimer, but serves as a transcriptional silencer in the presence of unidentified double and single stranded DNA-binding proteins. To address this apparent paradox, the current study examined the effect of two classes of candidate comodulatory proteins, COUP-TF (chicken ovalbumin upstream promoter transcriptional factor) and the corepressor SMRT (silencing mediator of retinoic acid receptor and thyroid receptor). The expression of COUP-TF was detected by Western and Northern blots in a preadipocyte 3T3-L1 cell model during periods corresponding to increased LPL transcription. Cotransfection of COUP-TF expression constructs in the renal epithelial

293T cell line significantly increased transcription from the LPL promoter in synergy with PPARgamma2/RXRalpha heterodimers. The COUP-TFII (ARP-1) protein specifically bound the LPL PPAR recognition element inelectromobility shift assays and interacted directly with the ligand-binding domain of PPARgamma in pull-down experiments. In contrast, cotransfection of SMRT repressed PPARgamma2/ RXRalpha-mediated LPL transcription in the absence or presence of COUP-TFII (ARP-1). The interaction between PPARgamma2 and SMRT localized to the receptor-interactive domain 2 (amino acids 1260-1495) of the SMRT protein based on cotransfection and pull-down assays. These in vitro data indicate that COUP-TF proteins and SMRT modulate PPARgamma-mediated LPL transcription in the 293T cell line.

ACCESSION NUMBER: 1999196128 MEDLINE
DOCUMENT NUMBER: 99196128 PubMed ID: 10098492
TITLE: A corepressor and chicken ovalbumin upstream promoter transcriptional factor proteins modulate peroxisome proliferator-activated receptor-gamma2/retinoid X receptor alpha-activated transcription from the murine lipoprotein lipase promoter.
AUTHOR: Robinson C E; Wu X; Nawaz Z; Onate S A; Gimble J M
CORPORATE SOURCE: Zoology Department, University of Oklahoma, Norman 73019, USA.
CONTRACT NUMBER: CA-50898 (NCI)
SOURCE: ENDOCRINOLOGY, (1999 Apr) 140 (4) 1586-93.
Journal code: EGZ; 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 19990426
Entered Medline: 19990415

L15 ANSWER 34 OF 92 MEDLINE

AB The Drosophila ecdysone receptor (EcR)/ultraspiracle (USP) heterodimer is a key regulator in molting and metamorphoric processes, activating and repressing transcription in a sequence-specific manner. Here, we report the isolation of an EcR-interacting protein, SMRTER, which is structurally divergent but functionally similar to the vertebrate nuclear corepressors SMRT and N-CoR. SMRTER mediates repression by interacting with Sin3A, a repressor known to form a complex with the histone deacetylase Rpd3/HDAC. Importantly, we identify an EcR mutant allele that fails to bind SMRTER and is characterized by developmental defects and lethality. Together, these results reveal a novel nuclear receptor cofactor that exhibits evolutionary conservation in the mechanism to achieve repression and demonstrate the essential role of repression in hormone signaling.

ACCESSION NUMBER: 1999417957 MEDLINE
DOCUMENT NUMBER: 99417957 PubMed ID: 10488333
TITLE: SMRTER, a Drosophila nuclear receptor coregulator, reveals that EcR-mediated repression is critical for development.
AUTHOR: Tsai C C; Kao H Y; Yao T P; McKeown M; Evans R M
CORPORATE SOURCE: Gene Expression Lab, Salk Institute, La Jolla, California 92037, USA.
CONTRACT NUMBER: GM26444 (NIGMS)

HD27183 (NICHD)
SOURCE: MOLECULAR CELL, (1999 Aug) 4 (2) 175-86.
Journal code: C5E; 9802571. ISSN: 1097-2765.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF175223
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991012

L15 ANSWER 37 OF 92 MEDLINE
AB On positive thyroid hormone response elements (pTREs), thyroid hormone receptor (TR) binding to DNA in the absence of ligand (thyroid hormone, T3) decreases transcription (silencing). Silencing is due to a family of recently described nuclear corepressor proteins (NCoR and SMRT) which bind to the CoR box in the hinge region of TR. Ligand-dependent activation of TR is associated with displacement of corepressors and recruitment of coactivating proteins. Resistance to thyroid hormone (RTH) is due to mutations in the beta isoform of the thyroid hormone receptor (TR-beta). To date, three RTH mutations reportedly with near-normal T3 binding (A234T, R243Q, and R243W) have been described in or near the CoR box. To determine the mechanism of RTH caused by these mutants, the interaction of wild type (wt) and mutant TRs with the corepressor, NCoR, and the coactivator, SRC-1, was tested in gel-shift assays. As expected, NCoR bound wt TR in the absence of T3 and dissociated from TR with increasing T3 concentration. SRC-1 failed to bind wt TR in the absence of T3, but bound to TR with increasing avidity as T3 concentrations rose. At no T3 concentration did both NCoR and SRC-1 bind to wt TR, indicating that their binding to TR was mutually exclusive. Hinge mutants bound NCoR normally in the absence of T3; however, dissociation of NCoR and recruitment of SRC-1 was markedly impaired except at very high T3 concentrations. Importantly, hinge mutant TRs when complexed to DNA bound T3 poorly despite their near-normal T3 binding in solution. These binding studies correlated with functional assays showing defective transactivation of pTREs by hinge mutants except at high T3 concentrations. Thus, we describe a novel mechanism of RTH whereby TR hinge mutants selectively affect T3 binding when complexed to DNA, and prevent NCoR dissociation from TR. Our data also suggest that solution T3 binding by RTH mutants may not accurately reflect physiologically relevant T3 binding by TR when bound to DNA.
ACCESSION NUMBER: 1999023934 MEDLINE
DOCUMENT NUMBER: 99023934 PubMed ID: 9804773
TITLE: Defective release of corepressor by hinge mutants of the thyroid hormone receptor found in patients with resistance to thyroid hormone.
AUTHOR: Safer J D; Cohen R N; Hollenberg A N; Wondisford F E
CORPORATE SOURCE: Thyroid Unit, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts 02215, USA.
CONTRACT NUMBER: DK-02423 (NIDDK)
DK-43653 (NIDDK)
DK-49126 (NIDDK)

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Nov 13) 273 (46) 30175-82.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981208

L15 ANSWER 38 OF 92 MEDLINE
AB Many transcription factors function by repressing gene transcription. For a variety of these transcription factors the ability to physically recruit auxiliary proteins, denoted corepressors, is crucial for the ability to silence gene expression. We and others have previously implicated the SMRT corepressor in the actions of the PLZF transcription factor and in the function of its oncogenic derivative, PLZF-retinoic acid receptor (RARalpha), in promyelocytic leukemia. We report here that PLZF, and a structurally similar transcriptional repressor, BCL-6, can interact with a variety of corepressor proteins in addition to SMRT, including the mSin3A protein and (for PLZF) histone deacetylase-1. Unexpectedly, these additional interactions with corepressor components are nonequivalent for these otherwise similar oncoproteins, suggesting that transcriptional repression by BCL-6 and by PLZF may differ in mechanism. Furthermore, we demonstrate that the oncogenic PLZF-RARalpha chimera lacks several important corepressor interaction sites that are present in the native PLZF protein. Thus the t(11;17) translocation that creates the PLZF-RARalpha chimera generates an oncoprotein with potentially novel regulatory properties distinct from those of either parental protein. Our results demonstrate that otherwise similar transcription factors can differ notably in their interactions with the corepressor machinery.
ACCESSION NUMBER: 1998438551 MEDLINE
DOCUMENT NUMBER: 98438551 PubMed ID: 9765306
TITLE: Components of the SMRT corepressor complex exhibit distinctive interactions with the POZ domain oncoproteins PLZF, PLZF-RARalpha, and BCL-6.
AUTHOR: Wong C W; Privalsky M L
CORPORATE SOURCE: Section of Microbiology, Division of Biological Sciences, University of California, Davis, California 95616, USA.
CONTRACT NUMBER: R01 DK-53528 (NIDDK)
R37 CA-53394 (NCI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Oct 16) 273 (42) 27695-702.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981106

L15 ANSWER 42 OF 92 CAPLUS COPYRIGHT 2001 ACS

AB Nuclear hormone receptors are ligand-regulated transcription factors that play crit. roles in metazoan homeostasis, development, and reprodn. Many nuclear hormone receptors exhibit bimodal transcriptional properties and can either repress or activate the expression of a given target gene. Repression appears to require a phys. interaction between a receptor and a corepressor complex contg. the SMRT/TRAC or N-CoR/RIP13 polypeptides. We wished to better elucidate the rules governing the assocn. of receptors with corepressors. We report here that different receptors interact with different domains in the SMRT and N-CoR corepressors and that these divergent interactions may therefore contribute to distinct repression phenotypes. Intriguingly, different isoforms of a single nuclear hormone receptor class also differ markedly in their interactions with corepressors, indicative of their nonidentical actions in cellular regulation. Finally, we present evidence that combinatorial interactions between different receptors can, through the formation of heterodimeric receptors, result in novel receptor-corepressor interactions not obsd. for homomeric receptors.

ACCESSION NUMBER: 1998:646683 CAPLUS
DOCUMENT NUMBER: 129:340480
TITLE: Transcriptional silencing is defined by isoform- and heterodimer-specific interactions between nuclear hormone receptors and corepressors
AUTHOR(S): Wong, Chi-Wai; Privalsky, Martin L.
CORPORATE SOURCE: Section of Microbiology, Division of Biological Sciences, University of California at Davis, Davis, CA, 95616, USA
SOURCE: Mol. Cell. Biol. (1998), 18(10), 5724-5733
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

L15 ANSWER 45 OF 92 MEDLINE

AB Several lines of evidence indicate that the nuclear receptor corepressor (N-CoR) complex imposes ligand dependence on transcriptional activation by the retinoic acid receptor and mediates the inhibitory effects of estrogen receptor antagonists, such as tamoxifen, suppressing a constitutive N-terminal, Creb-binding protein/coactivator complex-dependent activation domain. Functional interactions between specific receptors and N-CoR or SMRT corepressor complexes are regulated, positively or negatively, by diverse signal transduction pathways. Decreased levels of N-CoR correlate with the acquisition of tamoxifen resistance in a mouse model system for human breast cancer. Our data suggest that N-CoR- and SMRT-containing complexes act as rate-limiting components in the actions of specific nuclear receptors, and that their actions are regulated by multiple signal transduction pathways.

ACCESSION NUMBER: 1998169472 MEDLINE
DOCUMENT NUMBER: 98169472 PubMed ID: 9501191
TITLE: Diverse signaling pathways modulate nuclear receptor recruitment of N-CoR and SMRT complexes.
AUTHOR: Lavinsky R M; Jepsen K; Heinzel T; Torchia J; Mullen T M; Schiff R; Del-Rio A L; Ricote M; Ngo S; Gemsch J; Hilsenbeck S G; Osborne C K; Glass C K; Rosenfeld M G; Rose

D W
CORPORATE SOURCE: Howard Hughes Medical Institute, Department and School of Medicine, University of California at San Diego, La Jolla, CA 92093-0648, USA.
CONTRACT NUMBER: P30CA54174 (NCI)
P50CA58183 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Mar 17) 95 (6) 2920-5.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980422
Last Updated on STN: 19980422
Entered Medline: 19980410

L15 ANSWER 48 OF 92 MEDLINE
AB The thyroid hormone receptor splice variant, alpha2, is unable to bind thyroid hormone (T3) and has been proposed to function as an endogenous inhibitor of T3 action. In this report, we examined further the DNA sequence requirements for alpha2 binding to thyroid hormone response elements (TREs) in an attempt to identify response elements that mediate potent inhibition by alpha2. Heterodimers of alpha2 and retinoid X receptor were found to bind to a subset of TREs (DR4, direct repeats spaced by 4 bp) in which selected flanking and spacer sequences enhanced interactions with the AGGTCA core binding sequence. Despite the optimization of the TRE-binding sites, alpha2 remained a weak dominant negative inhibitor of TRE-driven transcription. A promoter interference assay was also developed for testing inhibition by alpha2. In these studies, alpha2 blocked gene transcription, but it required cotransfected retinoid X receptor, and it was not as potent as unliganded thyroid hormone receptors. These results led to the hypothesis that alpha2 might be deficient in interactions with nuclear receptor corepressors. Consistent with this view, alpha2 did not silence basal transcription in its native form or when linked to Gal4. Alpha2 also failed to interact with corepressors (NCoR and SMRT) in both gel shift assays and mammalian two-hybrid assays. We conclude that alpha2 is a weak antagonist of thyroid hormone action because it binds weakly to a limited repertoire of response elements, and it does not interact with corepressors. Thus, alpha2 may be able to compete with thyroid hormone receptors for binding to a limited group of target sites, but it is not able to actively inhibit transcription.
ACCESSION NUMBER: 1998224540 MEDLINE
DOCUMENT NUMBER: 98224540 PubMed ID: 9564869
TITLE: The thyroid hormone receptor variant alpha2 is a weak antagonist because it is deficient in interactions with nuclear receptor corepressors

AUTHOR: Tagami T; Kopp P; Johnson W; Arseven O K; Jameson J L
CORPORATE SOURCE: Division of Endocrinology, Metabolism, and Molecular Medicine, Northwestern University Medical School, Chicago, Illinois 60611, USA.

CONTRACT NUMBER: DK-42144 (NIDDK)
SOURCE: ENDOCRINOLOGY, (1998 May) 139 (5) 2535-44.
Journal code: EGZ; 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980520
Last Updated on STN: 19980520
Entered Medline: 19980508

L15 ANSWER 55 OF 92 MEDLINE
AB Previously, we defined a novel class of ligands for the human progesterone receptor (PR) which function as mixed agonists. These compounds induce a conformational change upon binding the receptor that is different from those induced by agonists and antagonists. This establishes a correlation between the structure of a ligand-receptor complex and its transcriptional activity. In an attempt to define the cellular components which distinguish between different ligand-induced PR conformations, we have determined, by using a mammalian two-hybrid assay, that the nuclear receptor corepressor (NCoR) and the silencing mediator for retinoid and thyroid hormone receptor (SMRT) differentially associate with PR depending upon the class of ligand bound to the receptor. Specifically, we observed that the corepressors preferentially associate with antagonist-occupied PR and that overexpression of these corepressors suppresses the partial agonist activity of antagonist-occupied PR. Binding studies performed in vitro, however, reveal that recombinant SMRT can interact with PR in a manner which is not influenced by the nature of the bound ligand. Thus, the inability of SMRT or NCoR to interact with agonist-activated PR when assayed in vivo may relate more to the increased affinity of PR for coactivators, with a subsequent displacement of corepressors, than to an inherent low affinity for the corepressor proteins. Previous work from other groups has shown that 8-bromo-cyclic AMP (8-bromo-cAMP) can convert the PR antagonist RU486 into an agonist and, additionally, can potentiate the transcriptional activity of agonist-bound PR. In this study, we show that exogenous expression of NCoR or SMRT suppresses all 8-bromo-cAMP-mediated potentiation of PR transcriptional activity. Further analysis revealed that 8-bromo-cAMP addition decreases the association of NCoR and SMRT with PR. Thus, we propose that 8-bromo-cAMP-mediated potentiation of PR transcriptional activity is due, at least in part, to a disruption of the interaction between PR and the corepressors NCoR and SMRT. Cumulatively, these results suggest that NCoR and SMRT expression may play a pivotal role in PR pharmacology.
ACCESSION NUMBER: 1998147776 MEDLINE
DOCUMENT NUMBER: 98147776 PubMed ID: 9488452
TITLE: The nuclear corepressors NCoR and SMRT are key regulators of both ligand- and 8-bromo-cyclic AMP-dependent transcriptional activity of the human progesterone receptor.
AUTHOR: Wagner B L; Norris J D; Knotts T A; Weigel N L; McDonnell D P
CORPORATE SOURCE: Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, North Carolina 27710,

USA.
CONTRACT NUMBER: DK50494 (NIDDK)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1998 Mar) 18 (3) 1369-78.
Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980326
Last Updated on STN: 19980326
Entered Medline: 19980319

L15 ANSWER 59 OF 92 MEDLINE
AB The human retinoic acid receptor alpha (hRAR alpha) exhibits cell-specific transcriptional activity. Previously, it was shown that in the absence of hormone the wild-type receptor is a transcriptional silencer in L cells, whereas it lacks silencing function and is a weak activator in CV1 cells. Addition of hormone leads to a further increase in transactivation in CV1 cells. Thus, the retinoic acid response mediated by RAR alpha is weak in these cells. It was shown that the CV1-specific effect is due to the receptor C terminus. We show, that the failure of silencing by RAR is not due to a general lack of corepressors in CV1 cells, since the silencing domain of RAR is functionally active and exhibits active repression in these cells. Furthermore, we show that the conserved AF2/tau c activation function of RAR is responsible for the cell-specific inhibition of silencing. Thereby, the CV1 cell specificity was abolished by replacing AF2/tau c of RAR with the corresponding sequence of the thyroid hormone receptor. Thus, we find a new role of the C-terminal conserved activation function AF2/tau c in that, specifically, the RAR AF2/tau c-sequence is able to prevent silencing of RAR in a cell-specific manner. In addition, we show that the inhibitory effect of AF2/tau c in CV1 cells can be overcome by expression of the corepressor SMRT (silencing mediator of retinoic acid and thyroid hormone receptor), but not by that of N-CoR (nuclear receptor corepressor). The expression of these two corepressors, however, had no measurable effect on RAR-mediated silencing in L cells. Thus, the expression of a corepressor can lead to a dramatic increase of hormonal response in a cell-specific manner.
ACCESSION NUMBER: 1998204547 MEDLINE
DOCUMENT NUMBER: 98204547 PubMed ID: 9544986
TITLE: Cell-specific inhibition of retinoic acid receptor-alpha silencing by the AF2/tau c activation domain can be overcome by the corepressor SMRT, but not by N-CoR.
AUTHOR: Baniahmad A; Dressel U; Renkawitz R
CORPORATE SOURCE: Genetisches Institut der Justus-Liebig Universitat, Giessen, Germany.. Aria.Baniahmad@Gen.Bio.Uni-Giessen.de
SOURCE: MOLECULAR ENDOCRINOLOGY, (1998 Apr) 12 (4) 504-12.
Journal code: NGZ; 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980713
Last Updated on STN: 19980713
Entered Medline: 19980630

L15 ANSWER 65 OF 92 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 7
AB A novel receptor-interacting factor, referred to herein as SMRT [silencing mediator (co-repressor) for retinoic acid receptor (RAR) and thyroid hormone receptor (TR)] is provided. SMRT exist as 2 alternatively spliced isoforms, a long form 1495 amino acids in length and a shorter form with residues 1330-1375 deleted. SMRT is a novel protein whose assocn. with RAR and TR both in soln. and on DNA response elements is destabilized by ligand. The interaction of SMRT with mutant receptors correlates with the transcriptional silencing activities of receptors. In vivo, SMRT functions as a potent co-repressor. A GAL4 DNA-binding domain (DBD) fusion of SMRT behaves as a frank repressor of a GAL4-dependent reporter. Together, these data identify a novel class of cofactor which is believed to represent an important mediator of hormone action.
ACCESSION NUMBER: 1997:265596 CAPLUS
DOCUMENT NUMBER: 126:247575
TITLE: Transcriptional co-repressor SMRT that interacts with nuclear hormone receptors and its uses to regulate hormone receptors and identify modulating ligands
INVENTOR(S): Evans, Ronald M.; Chen, J. Don
PATENT ASSIGNEE(S): Salk Institute for Biological Studies, USA
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9709418	A1	19970313	WO 1996-US12371	19960724
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2230858	AA	19970313	CA 1996-2230858	19960724
AU 9666398	A1	19970327	AU 1996-66398	19960724
AU 729344	B2	20010201		
EP 871704	A1	19981021	EP 1996-926156	19960724
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11511726	T2	19991012	JP 1996-521317	19960724

PRIORITY APPLN. INFO.: US 1995-522726 A 19950901
WO 1996-US12371 W 19960724

L15 ANSWER 70 OF 92 MEDLINE
AB Nuclear hormone receptors are ligand-regulated transcription factors that modulate gene expression in response to small, hydrophobic hormones, such as retinoic acid and thyroid hormone. The thyroid hormone and retinoic acid receptors typically repress transcription in the absence of hormone and activate it in the presence of

hormone. Transcriptional repression is mediated, in part, through the ability of these receptors to physically associate with ancillary polypeptides called corepressors. We wished to understand the mechanism by which corepressors are recruited to unliganded nuclear hormone receptors and are released on the binding of hormone. We report here that an alpha-helical domain located at the thyroid hormone receptor C terminus appears to undergo a hormone-induced conformational change required for release of corepressor and that amino acid substitutions that abrogate this conformational change can impair or prevent corepressor release. In contrast, retinoid X receptors appear neither to undergo an equivalent conformational alteration in their C termini nor to release corepressor in response to cognate hormone, consistent with the distinct transcriptional regulatory properties displayed by this class of receptors.

ACCESSION NUMBER: 97459713 MEDLINE
DOCUMENT NUMBER: 97459713 PubMed ID: 9315673
TITLE: A conformational switch in nuclear hormone receptors is involved in coupling hormone binding to corepressor release.
COMMENT: Erratum in: Mol Cell Biol 1998 Dec;18(12):7603
AUTHOR: Lin B C; Hong S H; Krig S; Yoh S M; Privalsky M L
CORPORATE SOURCE: Division of Biological Sciences, University of California at Davis, 95616, USA.
CONTRACT NUMBER: CA53394 (NCI)
T32-GM08343 (NIGMS)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1997 Oct) 17 (10) 6131-8.
Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971105
Last Updated on STN: 20000303
Entered Medline: 19971023

L15 ANSWER 73 OF 92 MEDLINE DUPLICATE 8
AB SMRT (silencing mediator of retinoic acid and thyroid hormone receptor) and N-CoR (nuclear receptor corepressor) are two related transcriptional corepressors that contain separable domains capable of interacting with unliganded nuclear receptors and repressing basal transcription. To decipher the mechanisms of receptor interaction and transcriptional repression by SMRT/N-CoR, we have characterized protein-protein interacting surfaces between SMRT and nuclear receptors and defined transcriptional repression domains of both SMRT and N-CoR. Deletional analysis reveals two individual nuclear receptor domains necessary for stable association with SMRT and a C-terminal helix essential for corepressor dissociation. Coordinately, two SMRT domains are found to interact independently with the receptors. Functional analysis reveals that SMRT contains two distinct repression domains, and the corresponding regions in N-CoR also repress basal transcription. Both repression domains in SMRT and N-CoR interact weakly with mSin3A, which in turn associates with a histone deacetylase HDAC1 in a mammalian two-hybrid assay. Far-Western analysis demonstrates a direct protein-protein

interaction between two N-CoR repression domains with mSin3A. Finally we demonstrate that overexpression of full-length SMRT further represses basal transcription from natural promoters. Together, these results support a role of SMRT/N-CoR in corepression through the utilization of multiple mechanisms for receptor interactions and transcriptional repression.

ACCESSION NUMBER: 1998075888 MEDLINE
DOCUMENT NUMBER: 98075888 PubMed ID: 9415406
TITLE: Characterization of receptor interaction and transcriptional repression by the corepressor SMRT.
AUTHOR: Li H; Leo C; Schroen D J; Chen J D
CORPORATE SOURCE: Department of Pharmacology and Molecular Toxicology, University of Massachusetts Medical School, Worcester 01655-0126, USA.
SOURCE: MOLECULAR ENDOCRINOLOGY, (1997 Dec) 11 (13) 2025-37. Journal code: NGZ; 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980224
Last Updated on STN: 19980224
Entered Medline: 19980210

L15 ANSWER 74 OF 92 MEDLINE
AB Chicken ovalbumin upstream promoter-transcription factors (COUP-TFs) are orphan receptors that belong to the steroid/thyroid hormone receptor (TR) superfamily and can repress the transcriptional activity of several target genes; however, the precise mechanism of this repression is unknown. Transfection of a Gal4 DNA-binding domain fused to the putative ligand-binding domain of COUP-TFI (Gal4-COUP-TFI) significantly represses the basal transcriptional activity of a reporter gene containing Gal4-binding sites. Cotransfection of COUP-TFI can relieve the Gal4-COUP-TFI repression in a dose-dependent manner. In contrast, COUP-TFI delta35, which lacks the repressor domain (the C-terminal 35 amino acids), fails to relieve this repression. This finding suggests that the repressor domain of COUP-TFI may squelch a limiting amount of corepressor in HeLa cells. In addition, increasing concentrations of TRbeta also can relieve the COUP-TFI repression in a hormone-sensitive manner. Similarly, overexpression of increasing concentration of COUP-TFI, but not COUP-TFI delta35, can squelch the silencing activity of the unliganded TRbeta. Collectively, these results indicate that COUP-TFI and TRbeta share a common corepressor(s) for their silencing activity. To determine which corepressor is involved in the COUP-TF-silencing activity, we used a yeast two-hybrid and in vitro GST pull-down assays to demonstrate that COUP-TFI can interact with the fragment of N-CoR (nuclear receptor-corepressor) encoding amino acids 921-2453 and the fragments of SMRT (silencing mediator for retinoic acid receptor and TR) encoding amino acids 29-564 and 565-1289, respectively. Interestingly, the fragment of SMRT encoding amino acids 1192-1495, which strongly interacts with TRbeta, interacts very weakly with COUP-TFI. Furthermore, overexpression of N-CoR or SMRT potentiates the silencing activity of COUP-TFI and can relieve the

COUP-TFI-mediated squelching of Gal4-COUP-TFI activity. Therefore, our studies indicate that N-CoR and SMRT act as corepressors for the COUP-TFI silencing activity.

ACCESSION NUMBER: 97315061 MEDLINE
DOCUMENT NUMBER: 97315061 PubMed ID: 9171235
TITLE: Gene silencing by chicken ovalbumin upstream promoter-transcription factor I (COUP-TFI) is mediated by transcriptional corepressors, nuclear receptor-corepressor (N-CoR) and silencing mediator for retinoic acid receptor and thyroid hormone receptor (SMRT).
AUTHOR: Shibata H; Nawaz Z; Tsai S Y; O'Malley B W; Tsai M J
CORPORATE SOURCE: Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
CONTRACT NUMBER: DK-45641 (NIDDK)
HD-08188 (NICHD)
SOURCE: MOLECULAR ENDOCRINOLOGY, (1997 Jun) 11 (6) 714-24.
Journal code: NGZ; 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970805
Last Updated on STN: 20000303
Entered Medline: 19970724

L15 ANSWER 80 OF 92 MEDLINE DUPLICATE 9
AB The transcriptional corepressors SMRT and N-CoR function as silencing mediators for retinoid and thyroid hormone receptors. Here we show that SMRT and N-CoR directly interact with mSin3A, a corepressor for the Mad-Max heterodimer and a homolog of the yeast global-transcriptional repressor Sin3p. In addition, we demonstrate that the recently characterized histone deacetylase 1 (HDAC1) interacts with Sin3A and SMRT to form a multisubunit repressor complex. Consistent with this model, we find that HDAC inhibitors synergize with retinoic acid to stimulate hormone-responsive genes and differentiation of myeloid leukemia (HL-60) cells. This work establishes a convergence of repression pathways for bHLH-Zip proteins and nuclear receptors and suggests this type of regulation may be more widely conserved than previously suspected.

ACCESSION NUMBER: 97294381 MEDLINE
DOCUMENT NUMBER: 97294381 PubMed ID: 9150137
TITLE: Nuclear receptor repression mediated by a complex containing SMRT, mSin3A, and histone deacetylase.
AUTHOR: Nagy L; Kao H Y; Chakravarti D; Lin R J; Hassig C A; Ayer D E; Schreiber S L; Evans R M
CORPORATE SOURCE: The Salk Institute for Biological Studies, La Jolla, California 92037, USA.
CONTRACT NUMBER: GM26444 (NIGMS)
HD27183 (NICHD)
SOURCE: CELL, (1997 May 2) 89 (3) 373-80.
Journal code: CQ4; 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970620
Last Updated on STN: 19970620
Entered Medline: 19970606

L15 ANSWER 85 OF 92 MEDLINE

AB Steroid/thyroid hormone receptors are ligand-dependent transcription factors that regulate diverse aspects of growth, development, and homeostasis by binding as homodimers or heterodimers to their cognate DNA response elements to modulate transcription of target genes. Transactivation by steroid/ thyroid hormone receptors involves a conserved AF-2 domain located in the distal carboxy-terminus of the receptors. The existence of co-factors, termed co-activators or adapters, was first suggested by transcriptional squelching between progesterone receptors and estrogen receptors. Co-repressors were also postulated to contribute to the silencing function of unliganded thyroid hormone receptor (TR). The yeast two-hybrid system and Far-Western blotting have been used to identify several proteins that interact with members of the steroid/thyroid hormone receptor superfamily in a ligand-sensitive manner. Our laboratory cloned the first functional co-activator, termed steroid receptor co-activator-one (SRC-1), that appears to be a general co-activator for all steroid receptors tested and enhances transactivation of steroid hormone-dependent target genes. Subsequently, many more putative co-activators have been reported, including the SRC-1 related proteins, TIF2 and GRIP1, and other putative and unrelated co-activators such as ARA70, Trip1, RIP140, and TIF1. In addition, another co-activator, CREB-binding protein (CBP), has been shown to enhance steroid receptor-dependent target gene transcription. CBP and SRC-1 interact and synergistically enhance transcriptional activation by the ER and PR. Therefore, a ternary complex-consisting of CBP, SRC-1, and liganded steroid receptors-may form to increase the rate of hormone-responsive gene transcription. Similarly, co-repressors, such as SMRT and N-CoR, for TR and retinoic acid receptors (RAR) have been identified. The unliganded TR and RAR have been shown to inhibit basal promoter activity; this silencing of target gene transcription by unliganded receptors is mediated by these co-repressors. Collectively, available evidence supports the following model of steroid-responsive gene transcription. Upon binding of agonist the receptor changes its conformation in the ligand-binding domain that enables recruitment of co-activators, which allows the receptor to interact with the basal transcriptional machinery more efficiently and to activate transcription. In contrast, binding of antagonists induces a different conformational change in the receptor. Although some antagonist-bound receptor can dimerize and bind to its cognate DNA element, it fails to dislodge the associated co-repressors, which results in a nonproductive interaction with the basal transcriptional machinery. Similarly, the TR and RAR associate with co-repressors in the absence of ligand, thereby resulting in a negative interaction with the transcriptional machinery that silences target gene expression. In the case of mixed agonist/antagonists, such as 4-hydroxytamoxifen, activation of gene transcription may depend on the relative ratio of co-activators and

co-repressors in the cell or cell-specific factors that determine the relative agonistic or antagonistic potential of different compounds. These co-activators and co-repressors appear to act as an accelerator and/or a brake that modulates transcriptional regulation of hormone-responsive target gene expression. Thus, the recent discovery of co-activators and co-repressors expands our knowledge of the mechanisms of steroid receptor action.

ACCESSION NUMBER: 97381624 MEDLINE
DOCUMENT NUMBER: 97381624 PubMed ID: 9238851
TITLE: Role of co-activators and co-repressors in the mechanism of steroid/thyroid receptor action.
AUTHOR: Shibata H; Spencer T E; Onate S A; Jenster G; Tsai S Y; Tsai M J; O'Malley B W
CORPORATE SOURCE: Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
SOURCE: RECENT PROGRESS IN HORMONE RESEARCH, (1997) 52 141-64; discussion 164-5. Ref: 119
Journal code: R1D; 0404471. ISSN: 0079-9963.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970908
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L15 ANSWER 87 OF 92 MEDLINE DUPLICATE 12
AB Transcriptional repression represents an important component in the regulation of cell differentiation and oncogenesis mediated by nuclear hormone receptors. Hormones act to relieve repression, thus allowing receptors to function as transcriptional activators. The transcriptional corepressor SMRT was identified as a silencing mediator for retinoid and thyroid hormone receptors. SMRT is highly related to another corepressor, N-CoR, suggesting the existence of a new family of receptor-interacting proteins. We demonstrate that SMRT is a ubiquitous nuclear protein that interacts with unliganded receptor heterodimers in mammalian cells. Furthermore, expression of the receptor-interacting domain of SMRT acts as an antirepressor, suggesting the potential importance of splicing variants as modulators of thyroid hormone and retinoic acid signaling.

ACCESSION NUMBER: 96353857 MEDLINE
DOCUMENT NUMBER: 96353857 PubMed ID: 8755515
TITLE: SMRT isoforms mediate repression and anti-repression of nuclear receptor heterodimers.
AUTHOR: Chen J D; Umesono K; Evans R M
CORPORATE SOURCE: The Salk Institute for Biological Studies, Howard Hughes Medical Institute, La Jolla, CA 92037, USA.
CONTRACT NUMBER: CHD27183 (NICHD)
GM26444 (NIGMS)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Jul 23) 93 (15) 7567-71.
Journal code: PV3; 7505876. ISSN: 0027-8424.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
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